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# Endothelial progenitor cells in arthritis-associated vasculogenesis and atherosclerosis

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## Abstract

Vasculogenesis is the generation of vessels from endothelial progenitor cells (EPCs). Attenuated numbers and function of EPCs associated with defective vasculogenesis are present in rheumatoid arthritis (RA), scleroderma and other autoimmune-inflammatory diseases, which have significant relevance for increased cardio- and cerebrovascular morbidity and mortality in arthritis [1–5]. Stimulation of EPCs and vasculogenesis may be beneficial to prevent and manage atherosclerosis related to arthritis. [1–5].

### Keywords

Vasculogenesis; Atherosclerosis; Rheumatoid arthritis; Endothelial progenitor cells

## 1. Endothelial progenitor cells: their essential role in vasculogenesis

Vasculogenesis, the growth of new vessels from EPCs is involved in both prenatal and postnatal tissue development, as well as vascular repair and atherosclerosis [2,5–7]. EPCs have been described within the population of blood stem cells. EPCs express both hematopoietic markers, such as CD34 and CD133, as well as the type 2 vascular endothelial growth factor (VEGF) receptor (VEGFR-2 or Flk-1) and CXCR4 [5,6,7–9]. Under normal conditions, EPCs become mobilized from the bone marrow and they differentiate into mature endothelial cells (ECs) [6,7–9].

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**Conflicts of interest**
The authors have no conflict of interest to declare.

## 2. Impaired EPC functions and other mechanisms of defective vasculogenesis in arthritis

In RA, EPCs are localized within the synovium in apposition to synovial vessels [9]. EPCs also differentiate into ECs in RA, however, there is a relative deficiency of EPCs in RA, as well as in vascular diseases leading to defective vasculogenesis and revascularization [1,5,6]. In RA, there is an $\alpha_4\beta_1$ integrin/VCAM-1-mediated recruitment of EPCs from the blood into the synovium [6,10]. Thus, depletion of EPCs from the circulation indeed leads to impaired vasculogenesis in RA [6,10]. EPCs derived from RA patients exert attenuated migratory capacity in response to VEGF [6,11]. Defective vasculogenesis may correlate with disease activity as the amount of EPCs in patients with active RA was significantly lower than that in patients with inactive disease [5]. Furthermore, the number of circulating EPCs were inversely correlated with the disease activity scale (DAS) index [5].

Among chemokines, stromal-derived factor 1 (SDF-1)/CXCL12 plays a major role in EPC recruitment to developing or injured tissues [6,7,12]. Most EPCs express the CXCR4 chemokine receptor and migrate in response to its ligand, SDF-1/CXCL12 [2,19]. SDF-1/CXCL12 induces the revascularization of ischemic tissues, such as the myocardium in coronary disease or the arthritic synovium [13]. Under ischemic conditions, hypoxia and hypoxia-inducible factor 1 (HIF-1) acts in part via SDF-1/CXCL12-mediated pathway during EPC recruitment to injured vessels [13]. Thus, SDF-1/CXCL12 may serve as a “molecular hub” that modulates vasculogenesis, as well as angiogenesis [12].

Among other regulators of vasculogenesis, interleukin-6 (IL-6) stimulates EPC migration and Matrigel tube formation [14]. E-selectin is also involved in EPC recruitment and soluble E-selectin reversed impaired vasculogenesis in an ischemic limb model [15]. Thus, some angiogenic mediators may also stimulate vasculogenesis. Despite the abundant production of vasculogenic and angiogenic chemokines, cytokines and adhesion receptors, vasculogenesis is still impaired in RA [5,6,14,15].

## 3. Accelerated atherosclerosis in RA: clinical relevance of impaired vasculogenesis

Accelerated atherosclerosis and increased cardiovascular morbidity and mortality have been associated with RA [3,4]. Traditional Framingham risk factors, such as obesity, smoking, hypertension or diabetes, as well as inflammatory factors, such as increased production of CRP, homocysteine, oxidized LDL (oxLDL), anti-oxLDL and anti-hsp antibodies have been implicated in the pathogenesis of arthritis-associated vascular disease [2–4]. In addition, the depletion of circulating EPCs and defective vasculogenesis may also be linked to atherosclerosis in RA [6,16]. Reduced number and migratory acitivity of EPCs in RA may result in a poorer response of circulating EPCs to ischemia leading to stroke or myocardial infarction [5,6]. Endothelial dysfunction indicated by impaired flow-mediated vasodilation correlated with lower numbers and abnormal function of circulating EPCs [11]. Thus, the loss of EPCs in the circulation of RA patients may link synovial inflammation and increased cardiovascular morbidity and mortality.

## 4. Restoration of diminished vasculogenesis: therapeutic options

As indirect approach, therapies that increase circulating EPC numbers may themselves improve vasculogenesis. For example, antitumor necrosis factor α (TNF-α) therapy in RA resulted in the restoration of circulating EPC levels and function [5,17]. There have been reports that some biologics may increase the overall survival and decrease atherosclerosis in RA [3,4,18]. In a recent cohort, RA patients treated with anti-TNF biologics did not have a

lower incidence of myocardial infarction in comparison to classical DMARD-treated patients. However, the risk of infarction was significantly reduced in biologic-responder patients compared to nonresponders [19]. Certainly, anti-TNF agents, apart from stimulating EPC mobilization, exert multiple other effects that lead to the improvement of vascular disease in arthritis.

Direct infusions of EPCs may be used for the induction of neovascularization in therapeutic trials in certain vascular and inflammatory diseases associated with insufficient EPC number or function [1,20]. Clinical trials indicate that peripheral blood-derived EPCs integrate into newly formed vessels in animal models of limb ischemia, as well as in human obliterative atherosclerosis [1,6,20]. In the future, EPCs may be used to restore defective vasculogenesis in inflammatory diseases, such as RA.

## 5. Conclusion

Defective vasculogenesis based on decreased number and impaired functions of EPCs has been associated with RA. This involves NO-, integrin- and chemokine-dependent mechanisms. Abnormal vasculogenesis is involved, in part, in accelerated atherosclerosis and excess cardiovascular mortality seen in RA and other rheumatic diseases. Anti-TNF biologics may themselves restore EPC mobilization and functions leading to the normalization of vasculogenesis. In the future, direct EPC infusions currently undergoing clinical trials in atherosclerotic diseases may also be applied to arthritis patients.

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